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An improved synthesis of (20*S*)-camptothecin and its analogue via an asymmetric α-hydroxylation with a chiral organocatalyst

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ABSTRACT

An efficient and stereocontrolled synthesis of (20*S*)-camptothecin and an analogue has been developed. The key feature of this synthesis is the organocatalyzed asymmetric α-hydroxylation of the lactone precursor **4** to construct its stereocenter, providing tricyclic hydroxylactone **2** in 90% yield and with 88% enantioselectivity. The precursor **4** was efficiently synthesized from the known pyridine **5** in three steps.

1. Introduction

Camptothecin **1** (Fig. 1) is a pentacyclic natural alkaloid, which was originally isolated from *Camptothecin acuminate* (Xi Su, originating in China) by Wall et al. in 1966.[1] Camptothecin has attracted considerable interest from academic researchers, as well as scientists working in the pharmaceutical sector because of its unique chemical structure and inhibitory activity towards DNA topoisomerase I. Notably, several analogues of camptothecin, including topotecan and irinotecan, are currently progressing through clinical and preclinical trials for the treatment of Cancer.[2] Since Corey et al. reported the first synthesis of optically active camptothecin, many impressive total syntheses of camptothecin have been developed by numerous research groups.[3] Among these strategies, the B-ring approach represents the most efficient route for the construction of alkaloids belonging to the camptothecin family via the Friedlander condensation of the A ring fragment with the CDE ring fragment **2**.

The main challenges associated with the synthesis of **2** is the construction of the stereocenter at the C-20 position. The main approaches that have been developed to date for installing this stereogenic center, include chemical or enzymatic resolution;[4] chiral auxiliary-mediated ethylation;[5] asymmetric dihydroxylation;[6] and asymmetric cyanosilylation.[7] However, these approaches have been limited by requirement for the stoichiometric addition of an expensive chiral auxiliary, the use of a highly toxic reagent (OsO_4), or the low efficiency of the resolution.

Lactones can be readily converted into the corresponding α-hydroxy-lactones in an enantioselective manner by the direct oxidation of their α-position.[8,9] Our group reported[10a] a concise approach for the direct α-hydroxylation of **3** using a chiral oxaziridine in the presence of KHMDS, which provided **2** in 82% yield with moderate enantioselectivity. Recently, Nagasawa et al.[10b] reported that the stereochemistry at the C-20 position of camptothecin could be established by the α-hydroxylation of **3** using a guanidine-urea bifunctional organocatalyst (Nagasawa's catalyst) in 93% yield and with 84% ee. Unfortunately, the preparation of precursor **3** suffers from low efficiency (13 steps), high-cost, and large amounts of waste.[11] Therefore, our aim was to use a synthetic approach involving Danishefsky's lactone **4**[12] with short reaction steps (6 steps) and low waste to establish the stereocenter of (20*S*)-camptothecin molecules by using Nagasawa's asymmetric α-hydroxylation strategy. Herein, we report the full details of our recent efforts towards the development of the synthesis of prochiral precursor **4**, and the total synthesis of (20*S*)-camptothecin and its analogue.

2. Results and discussion

The synthesis commenced from the known indolizine **5**, obtained from commercially available 1,3-acetonedicarboxylate through a three-step procedure.[12] Treatment of **5** under Danishefsky's conditions (CH_2O, H_2SO_4, dioxane/H_2O) failed to afford the desired lactone **6**.[13] Fortunately, we found that lactone **6** can be easily achieved by treatment of **5** with glacial acetic acid and concentrated HCl in 77% yield, along with approximately 20% of the partially hydrolyzed aromatic acid **7** (Scheme 1), which can be readily isolated from the mixture in 20% yield by acidic work-up. Subsequently, re-esterification of **7** with methanol in the presence of methanesulfonic acid afforded **5** in 90% yield. It is noteworthy that paraformaldehyde gave similar results as 37% formaldehyde did for this reaction.

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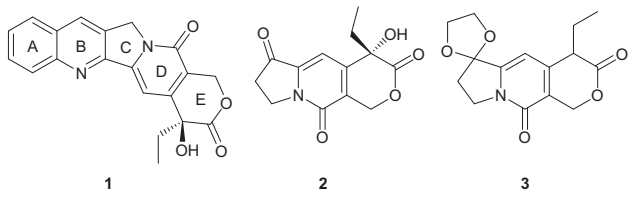
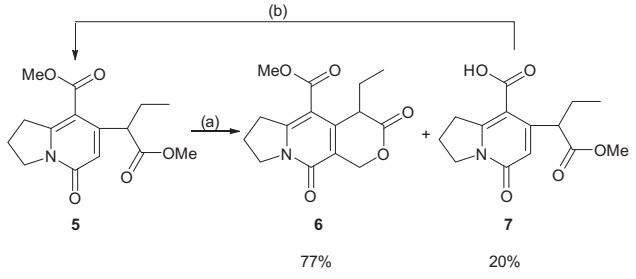


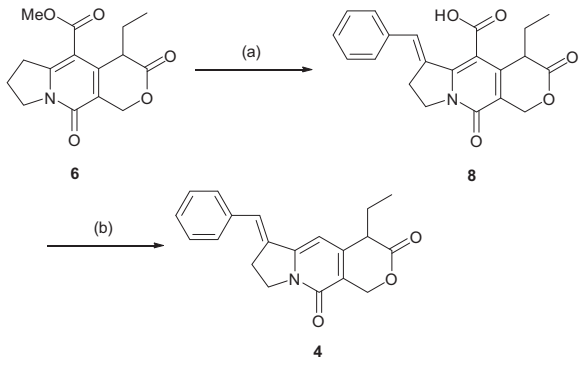
Figure 1. Structures of (20*S*)-camptothecin and its intermediates.

Functionalization of the benzylic position on the five-membered ring of **6** according to the general method of Danishefsky (NaHMDS, benzaldehyde, −70 °C), provided compound **8** in 90% yield with the concomitant hydrolysis of the methyl ester (Scheme 2). However, this procedure is not suitable for large-scale synthesis of the desired product **8** because of its requirement of low-temperature and low concentrations. We found that the reaction of **6** in DMF/THF instead of THF, in the presence of the PTC benzyltrimethylammonium chloride (TEBAC) at −40 °C afforded compound **8** in 89% yield. The subsequent decarboxylation of **8** in 48% aqueous HBr solution afforded **4** in 93% yield.

Continuing with this strategy, we investigated the asymmetric α-hydroxylation of lactone **4** using a direct asymmetric hydroxylation protocol. We initially conducted a series of screening experiments to optimize some of the key reaction parameters, including the catalyst, catalyst loading, temperature, reaction time, solvents and additives (Table 1). Jorgensen et al.[14] reported the first organocatalytic α-hydroxylation of β-keto esters using a cinchona-alkaloid derivative as a catalyst in the presence of an oxidant, which afforded the desired hydroxylated products in high yields and with moderate to high enantioselectivity.[9] Over the past decade, considerable research efforts have been directed towards the development of highly enantioselectivity catalysts for this reaction. It is highly desirable that the asymmetric catalysts used in these reactions can be readily prepared from simple starting materials to inspire their wider application within the synthetic chemistry community. Compound **4** failed to afford any of the desired hydroxylated product when we used quinine-based catalysts (Table 1, entries 1 and 2), suggesting that the reaction was occurring under biphasic conditions. With this in mind, we designed and synthesized two new cinchona alkaloids **13a** and **13b** as phase transfer catalysts (PTCs) for this reaction (Table 1, entries 3 and 4). The reaction proceeded smoothly in the presence of catalysts **13a** and **13b** to afford the desired product in 78% and 90% yields, respectively. However, the selectivity of this reaction remained poor to moderate (Table 1, entries 3 and 4). Encouraged by this result, we synthesized and evaluated some of Nagasawa's catalysts **14a–f**. These catalysts provided moderate to high enantioselective (61–75%). We subsequently investigated the effects of different substituents on the benzene ring of the catalyst. Among the different catalysts tested, compound **14a** was found to be the most effective one for this reaction, affording **9** in 81% yield and with 75% ee. These results therefore indicated that the size of the substituent group was critical to the success of the reaction.



Scheme 1. *Reagents and conditions*: (a) 37% CH_2O, AcOH, con. HCl, 80 °C, 77%, 14 h; (b) MeOH, $MeSO_3H$, reflux, 24 h, 90%.



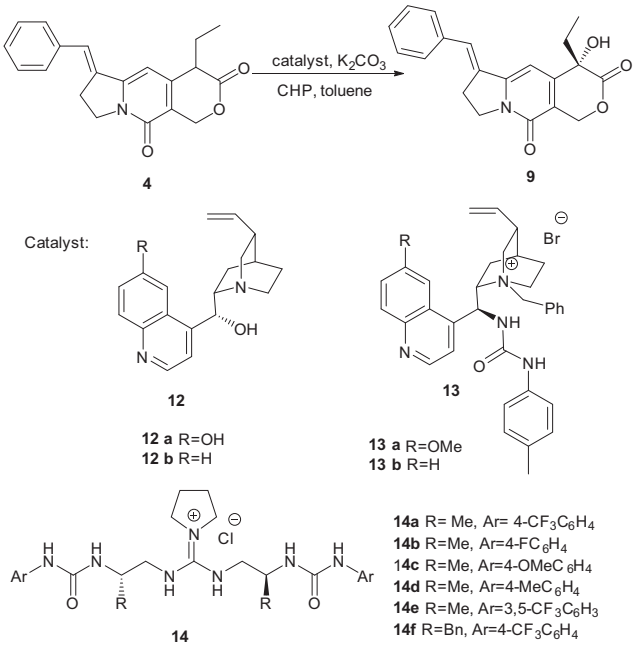
Scheme 2. *Reagents and conditions*: (a) benzaldehyde, NaHMDS, TEBAC, DMF/THF, −40 °C, 89%; (b) 48% HBr, 90 °C, 3 h, 93%.

Having identified compound **14a** as the most suitable catalyst for this transformation, we proceeded to investigate the optimization of this reaction (Table 2). A series of screening experiments revealed that the optimal reaction conditions were as follows: catalyst (10 mol %), potassium carbonate (1.2 equiv) and CHP (1.5 equiv), which was used as an oxidant, over 48 h.

We initially investigated the effects of temperature on the outcome of the α-hydroxylation reaction. Reducing the reaction temperature to −10 °C led to a considerable improvement in the ee value to 91%. However, this change was also accompanied by a decrease in the yield (Table 2, entry 1), with the desired product **9** being isolated in 27% yield together with the starting compound, which was recovered in 70% yield. It is noteworthy that the catalyst was recovered in 80% yield by flash column chromatography over silica gel. Furthermore, the recovered catalyst could be reused in this transformation, giving identical yields and enantioselectivities. Increasing the reaction temperature to 30 °C led to an increase in the yield, although this increase was accompanied with a decrease in the ee value to 67% (Table 2, entry 5). Based on these results, 20 °C was selected as the optimal reaction temperature. We then proceeded to screen the reaction against a variety of different solvents, including CH_2Cl_2, THF, $CHCl_3$, toluene, toluene/$CHCl_3$ and toluene/CH_2Cl_2. The results of these experiments revealed that the use of toluene led to good enantioselectivity and high yield (Table 2, entry 4), but also resulted in a sluggish reaction. We also investigated the use of a mixed solvent system composed of toluene/$CHCl_3$ with the aim of increasing the solubility of the starting material and product, and thereby reducing the reaction time (Table 2, entry 10). The use of this mixed solvent system provided **9** in 85% yield and with 84% ee. The results of numerous studies have shown that the use of an additive is crucial for obtaining good yields and enantioselectivities in α-hydroxylation reactions.[15] With this in mind, we investigated the use of several different additives to promote this reaction. Among the many additives tested, the use of 4 Å molecular sieves provided the best result in terms of the yield and enantioselectivity (Table 2, entry 12). CTAB and TBAB both afforded nearly racemic mixtures of the desired product (Table 2, entries 14 and 16). These results indicated that the additive was acting as a PTC.

The α-hydroxylation of **4** also resulted in the oxidation of the double bonds in benzylidene to give the undesired epoxide **11**, which subsequently underwent a base-mediated ring-opening reaction to afford the secondary alcohol **10** (Scheme 3). We therefore investigated the use of $HIO_4{\cdot}2H_2O$ to allow for the conversion of these unwanted byproducts to the desired product **9**. After 10 h

Table 1
Optimization of the α-hydroxylation reaction of **4** using a chiral phase transfer catalyst[a]



Entry	Catalyst	Solvent	Temp (°C)	e.e[b] (%)	Yield[c] (%)
1	**12a**	Toluene	20	–	–
2	**12b**	Toluene	20	–	–
3	**13a**	Toluene	20	47	78
4	**13b**	Toluene	20	19	90
5	**14a**	Toluene	20	75	81
6	**14b**	Toluene	20	67	80
7	**14c**	Toluene	20	70	65
8	**14d**	Toluene	20	73	82
9	**14e**	Toluene	20	64	80
10	**14f**	Toluene	20	61	68

[a] The reaction of **4** (1 mmol) with cumene hydroperoxide (CHP) (1.5 equiv) was conducted in the presence of catalyst (10 mol %) and K_2CO_3 (1.2 equiv) in toluene (5 mL) at 20 °C.
[b] The enantiomeric excess was determined by HPLC on a Daicel Chiralcel AD-H column eluting with a 4:1 (v/v) mixture of hexane and *i*-PrOH at 0.6 mL/min with a detection wavelength of 220 nm at 30 °C. *t*(major) = 66 min, *t*(minor) = 42 min.
[c] Isolated yield.

Table 2
Optimization of the reaction conditions with catalyst **14a**[a]

Entry	Temp (°C)	Solvent	Additive[b]	e.e.[c] (%)	Yield[d] (%)
1	−10	Toluene	–	91	27
2	0	Toluene	–	82	41
3	10	Toluene	–	76	65
4	20	Toluene	–	75	81
5	30	Toluene	–	67	85
6	20	DCM	–	60	79
7	20	THF	–	25	70
8	20	$CHCl_3$	–	69	77
9	20	DCM/toluene	–	82	80
10	20	$CHCl_3$/toluene	–	84	85
11	20	$CHCl_3$/toluene	β-CD	85	84
12	20	$CHCl_3$/toluene	4 Å M.S.	88	90
13	20	$CHCl_3$/toluene	$MgSO_4$	72	88
14	20	$CHCl_3$/toluene	CTAB	25	90
15	20	$CHCl_3$/toluene	SDS	73	90
16	20	$CHCl_3$/toluene	TBAB	5	89

[a] The reactions of **4** (1 mmol) with CHP (1.5 equiv) was conducted in the presence of catalyst (10%) and K_2CO_3 (1.2 equiv) in toluene (5 mL) at 20 °C.
[b] CTAB (hexadecyltrimethylammonium bromide), SDS (sodium dodecyl sulfate), β-CD (β-cyclodextrin) and TBAB (tetrabutylammonium bromide).
[c] The enantiomeric excess was determined by HPLC on a Daicel Chiralcel AD-H column eluting with a 4:1 (v/v) mixture of hexane and *i*-PrOH at 0.6 mL/min with a detection wavelength of 220 nm at 30 °C. *t*(major) = 66 min, *t*(minor) = 42 min.
[d] Isolated yield.

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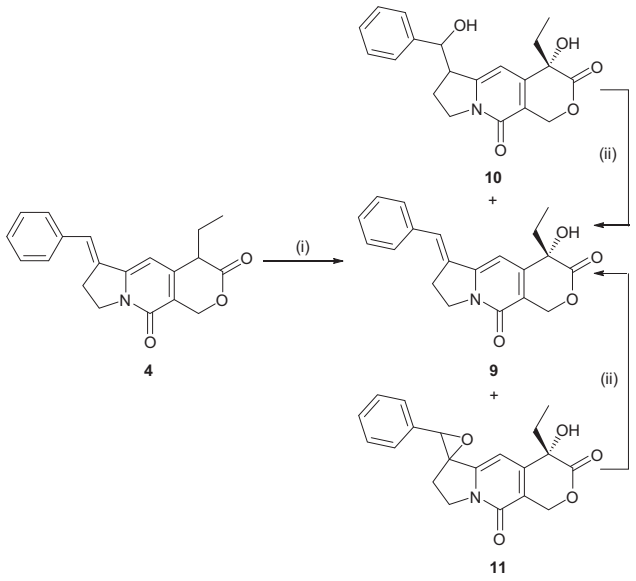
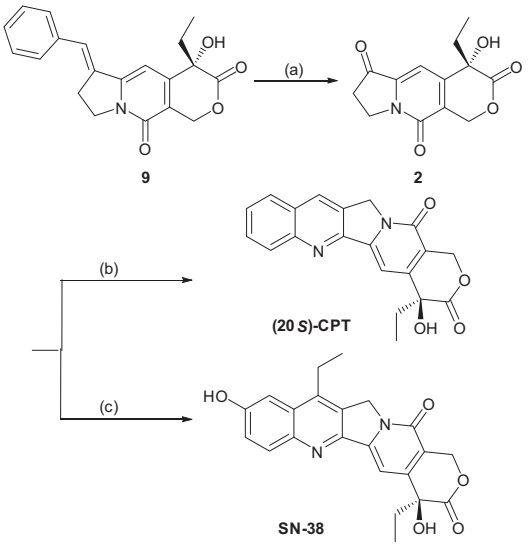


Scheme 3. Conversion of secondary alcohol **10** and epoxide **11** to **9**. *Reagents and conditions*: (i) catalyst **14a**, CHP, K_2CO_3, rt, 24 h; (ii) Amberlyst 15, NaI, acetone, rt, 5 h, 96%.

at room temperature, compounds **11** and **10** provided **9** in 90% yield, and the authenticity of this material was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analyses. A comparison of the commercial availability and cost of $HIO_4{\cdot}2H_2O$ with those of NaI and Amberlyst 15 resin led us to select the latter of these two systems as the best acid catalyst for this transformation. This reaction required no more than 5 h at room temperature to afford **9** in 96% isolated yield. It is noteworthy that the isolation of this product involved a simple filtration, which also allowed for the quantitative recovery of the Amberlyst 15 resin.

The penultimate step in this process required the oxidative cleavage of double bonds of the benzylidene moiety in compound **9** by ozonolysis. This reaction was carried out at −40 °C in CH_2Cl_2 for 0.5 h, affording **2** in 96% yield.



Scheme 4. *Reagents and conditions*: (a) O_3, CH_2Cl_2, −40 °C, 0.5 h, 96%; (b) 2-aminobenzaldehyde, TMSCl, DMF, 100 °C, 78%; (c) 1-(2-amino-5-hydroxyphenyl) propan-1-one, I_2, DMF, 80 °C, 80%.

Finally, the Friedlander condensation of **2** with 2-aminobenzaldehyde in the presence of TMSCl in DMF[16] afforded **1** in 78% yield and with 95% ee (Scheme 4), which was upgraded to 99% ee following a simple recrystallization from methanol/acetone (1:1, v/v). The reaction of **2** with 2-amino-5-hydroxypropiophenone under the known method[7] afforded **SN-38** in 80% yield with 99% ee.

3. Conclusion

In conclusion, we have developed a concise total synthesis of (20*S*)-camptothecin based on a mild and efficient α-hydroxylation reaction, which gave the desired α-hydroxyl lactone with high enantioselective and good yield. This route could be particularly beneficial for preparing analogs of (20*S*)-camptothecin, as well as providing a platform for the development of an alternative industrial-scale synthesis.

4. Experimental

4.1. General

All of the reagents and solvents used in this study were obtained from commercial sources and used without further purification. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as an internal standard. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer. Optical rotations were measured on a JASCO P1020 digital polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer, and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS were recorded on a Bruker microTOF spectrometer.

4.2. 4-Carbomethoxy-de-AB-deoxycamptothecin 6

A stirred mixture of compound **5** (58.6 g, 0.2 mol), acetic acid (105 mL), concentrated HCl (35 mL) and formalin (50 mL, 37%) was heated at 80 °C for 14 h. The mixture was cooled to 0 °C, then the reaction was neutralized with 10% NaOH, then methylene dichloride (100 mL) was added, and the aqueous phase was extracted with methylene dichloride (100 mL × 3). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate 1:1, v/v) to give **6** (45 g, 77%) as a white solid. The aqueous phase was adjusted to pH = 2–3 using 2 M HCl and the by-product **7** (11 g, 20%) was obtained by filtration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (d, J = 15.8 Hz, 1H), 5.13 (d, J = 15.8 Hz, 1H), 4.35 (dd, J = 9.0, 5.1 Hz, 1H), 4.28–4.11 (m, 2H), 3.86 (s, 3H), 3.62–3.33 (m, 2H), 2.23 (p, J = 7.4 Hz, 2H), 2.03–1.89 (m, 1H), 1.85–1.73 (m, 1H), 1.08 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 165.3, 157.9, 157.0, 146.2, 118.4, 109.0 65.5, 52.0, 49.6, 44.7, 34.7, 25.3, 20.8, 12.0.

Compound **7**: mp = 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 4.20 (t, J = 7.2 Hz, 2H), 4.10 (*t*, J = 6.8 Hz, 1H), 3.88 (s, 3H), 3.42–3.46 (m, 2H), 2.10–2.24 (m, 2H), 1.73–2.12 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

4.3. (*E*)-6-Benzylidene-4-ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-5-carboxylic acid 8

To a solution of tricyclic lactone **6** (5.0 g, 17.1 mmol), TEBAC (78 mg, 2%), and benzaldehyde (1.82 g, 17.1 mmol) in mixed solvent DMF/THF (15 mL/15 mL) at −40 °C was added NaHMDS (20.6 mL, 1 M in THF). The orange solution was allowed to warm

to room temperature for 24 h before it was quenched with 2 M HCl (20 mL). After an additional 1 h, the mixture was extracted with $CHCl_3$/methanol (10:1, v/v) (40 mL × 3), the organic phase combined, dried over $MgSO_4$, and the solvent was removed. The crude product was triturated with THF (20 mL × 3) to afford **8** (5.6 g, 89%) as a pale yellow solid. Mp >300 °C; IR (neat): ν_{max} (cm^{-1}) 2972, 1745, 1723, 1623, 1575, 1532, 1183, 1053, 689, 655; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38–7.45 (m, 5H), 7.19 (br s, 1H), 5.26 (dd, J = 9.6, 16.0 Hz, 2H), 4.04 (dd, J = 4.0, 7.2 Hz, 2H), 3.55 (m, 1H), 3.19 (m, 2H), 1.83 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 169.9, 167.3, 156.4, 145.8, 143.6, 135.4, 134.0, 130.0, 129.1, 128.7, 117.9, 107.0, 64.9, 46.5, 43.9, 27.4, 24.4, 11.7.; HRMS calcd for $C_{21}H_{19}NO_5$ $[M]^+$ m/z 365.1302, found m/z 365.1311.

4.4. (*E*)-6-Benzylidene-4-ethyl-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*,6*H*)-dione 4

A stirred solution of benzylidene acid **8** (7.3 g, 20 mmol) in 48% hydrobromic acid (50 mL) was heated at 90 °C for 3 h. The mixture was cooled to room temperature then the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (100 mL), washed with Sat. $NaHCO_3$ (20 mL × 3). The organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo, the crude product was crystallized from ethanol (25 mL) to afford benzylidene **4** (6.0 g, 93%) as a yellow crystals. Mp = 184.0–185.7 °C; IR (neat): ν_{max} (cm^{-1}) 3579, 3367, 1723, 1645, 1576, 1471, 1375, 1042, 844, 758, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.50 (m, 5H), 7.19 (br s, 1H), 6.45 (s, 1H), 5.47 (d, J = 16.0 Hz, 1H), 5.29 (d, J = 16.0 Hz, 1H), 4.29 (t, J = 4.0, 7.6 Hz, 2H), 3.50 (t, J = 6.4 Hz, 1H), 3.27 (dt, J = 2.4, 5.6 Hz, 2H), 2.01 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 157.6, 149.2, 146.8, 136.1, 135.0, 129.4, 129.2, 128.5, 126.2, 117.6, 96.7, 65.5, 47.2, 45.3, 27.0, 23.8, 11.5. HRMS calcd for $C_{20}H_{20}NO_3$ $[M+H]^+$ m/z 322.1443, found m/z 322.1436.

4.5. (*S*,*E*)-6-Benzylidene-4-ethyl-4-hydroxy-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*,6*H*)-dione 9

To a solution of benzylidene **4** (3.21 g, 10 mmol) in mixed solvent $CHCl_3$/toluene (10 mL/ 90 mL) were added .catalyst **14a** (0.63 g, 1 mmol), 4 Å MS (50 mg) and K_2CO_3 (1.65 g, 12 mmol) at room temperature. The mixture was cooled to 0 °C and stirred for 0.5 h, then cumene hydroperoxide (2.85 g, 15 mmol) was added. The mixture was heated to 20 °C for 48 h. The reaction was quenched by $Na_2S_2O_3$ solution, and the mixture was stirred at room temperature for 2 h. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 mL × 3), the organic layers combined, dried over Na_2SO_4, concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 1:1, v/v) to give **9** (2.8 g, 85%), the ee values of **9** was upgraded from 88% to 94% by recrystallized from ethyl acetate, determined by HPLC analysis, Daicel AD-H, column (25 cm × 4.6 mm × 5 μm), *n*-hexane/*i*-PrOH = 80:20, 0.6 mL/min, 220 nm, 30 °C, t_R(minor)=42 min, t_R (major) = 66 min. Mp = 197.7–198.4 °C. IR (neat): ν_{max} (cm^{-1}) 3359, 1739, 1635, 1546, 1450, 1163, 1042, 755, 691. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.50 (m, 5H), 7.27 (br s, 1H), 6.93 (s, 1H), 5.62 (d, J = 16.4 Hz, 1H), 5.20 (d, J = 16.4 Hz, 1H), 4.27 (m, 2H), 3.85 (br s, 1H), 3.27 (dt, J = 2.4, 5.6 Hz, 2H), 1.81 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 158.6, 150.1, 136.1, 134.3, 129.8, 129.5, 129.3, 127.9, 126.7, 95.2, 73.4, 67.0, 47.6, 32.0, 27.8, 8.4. HRMS calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$ m/z 338.1392, found m/z 338.1390.

4.6. (4′*S*)-4′-Ethyl-4′-hydroxy-3-phenyl-7′,8′-dihydrospiro[oxirane-2,6′-pyrano[3,4-*f*]indolizine]-3′,10′(1′*H*,4′*H*)-dione 11

The α-hydroxylation reaction was carried out under the same condition, the residue was purified by flash chromatography (petroleum ether/ethyl acetate 1:2, v/v) to give **11** (0.25 g, 5%), the compound **11** (0.25 g, 5%) was obtained by flash chromatography (ethyl acetate) and the recovery of catalyst **14a** (0.51 g, 80%) was obtained by CH_2Cl_2/ methanol, 10:1, v/v). Mp = 219–221 °C. IR (neat): ν_{max} (cm^{-1}) 3225, 2965, 1656, 1584, 1552, 1399, 1107, 1015, 908, 763, 688. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34–7.56 (m, 6H), 6.88 (s, 1H), 6.56 (s, 1H), 4.83 (d, J = 13.2 Hz, 1H), 4.68 (d, J = 13.2 Hz, 1H), 4.11 (t, J = 6.8 Hz, 2H), 3.23 (m, 2H), 1.88 (q, J = 7.2 Hz, 2H), 0.76 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9, 152.5, 150.4, 136.1, 134.8, 129.1, 128.9, 128.1, 125.5, 125.4, 110.5, 92.5, 79.3, 69.3, 46.5, 31.6, 27.3, 8.3. HRMS calcd for $C_{19}H_{20}NO_3$ $[M-CO_2+H]^+$ m/z 310.1443, found m/z 310.1447.

4.7. (4*S*)-4-Ethyl-4-hydroxy-6-(hydroxy(phenyl)methyl)-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*,6*H*)-dione 10

Mp >300 °C. IR (neat): ν_{max} (cm^{-1}) 3404, 2930, 1611, 1568, 1367, 1090, 989, 809, 683. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, J = 7.6 Hz, 2H), 7.44(t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.23 (s, 1H), 7.20 (s, 1H), 6.00 (s, 1H), 5.69 (dd, J = 3.2, 4.0 Hz, 1H), 4.76 (dd, J = 3.2, 8.4 Hz, 1H), 4.47 (dd, J = 3.2, 8.8 Hz, 1H), 4.10–4.02 (m, 3H), 3.17 (t, J = 6.0 Hz, 2H), 2.07 (q, J = 7.2 Hz, 1H), 1.93 (q, J = 7.2 Hz, 1H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 161.9, 156.4, 144.8, 136.4, 135.7, 129.3, 129.0, 128.1, 126.8, 124.3, 98.5, 80.0, 56.0, 48.9, 47.1, 31.5, 27.1, 9.4. HRMS calcd for $C_{20}H_{22}NO_5$ $[M+H]^+$ m/z 356.1498, found m/z 356.1490.

4.8. (*S*)-4-Ethyl-4-hydroxy-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione 2

A solution of α-hydroxylation lactone **9** (3.37 g, 10 mmol) in CH_2Cl_2 (100 mL) was cooled to–40 °C and a stream of ozone in oxygen was bubbled through. After the starting material had virtually disappeared (0.5 h), a stream of oxygen was bubbled through the reaction mixture for 15 min. The reaction mixture was treated with dimethyl sulfide (1.46 mL, 20 mmol) and allowed to warm to room temperature over 2 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate and water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give trione **2** (2.5 g, 96%) as a brown solid. The ee of **2** was increased from 94% to 99% by a single recrystallization using ethyl acetate, determined by HPLC analysis, Daicel AD-H, column (25 cm × 4.6 mm × 5 μm), *n*-hexane/ *i*-PrOH = 70:30, 1.0 mL/min, 220 nm, 30 °C, t_R(major) = 26.5 min, t_R (minor) = 54.7 min. Mp = 179–181 °C (lit. mp = 176–177 °C), $[\alpha]_D^{21.8}$ = +115.3 (*c* 0.62, $CHCl_3$) (lit. $[\alpha]_D^{20.0}$ +120.6 (*c* 0.62, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 5,63 (d, J = 16.8 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 4.35 (t, J = 6.8 Hz, 2H), 3.89 (br s, 1H), 2.98 (t, J = 6.0 Hz, 2H), 1.81 (q, J = 2.8, 4.4 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 173.1, 157.6, 149.2, 139.8, 124.4, 100.7, 72.2, 66.1, 42.1, 33.6, 31.6, 7.6.; HRMS calcd for $C_{13}H_{14}NO_5$ $[M+H]^+$ m/z 264.0872, found m/z 264.0870.

4.9. (20*S*)-Camptothecin 1[16]

Yield 78%. Mp = 264–265 °C (lit: 265–266 °C). IR (neat): ν_{max} (cm^{-1}). 3265, 2989, 2938, 1755, 1645, 1578, 1399, 1227, 1157, 1098, 1039, 997, 766, 723, 659. $[\alpha]_D^{20.4}$ +41.5 (c 0.2, $CHCl_3$/MeOH = 4:1), lit. $[\alpha]_D^{23}$ +42.0 (*c* 0.51, $CHCl_3$/MeOH = 4:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.10 (dd, J = 8.4, 11.2 Hz,

2H), 7.86 (t, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.34 (s, 1H), 6.53 (1H), 5.42 (s, 2H), 5.27 (s, 2H), 1.85 (m, 2 H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.9, 157.3 153.1, 150.5, 148.4, 146.0, 132.1, 130.9, 130.3, 129.5, 129.1, 128.3, 128.1, 119.7, 97.2, 72.9, 65.8, 50.7, 30.8, 8.4. HRMS calcd for $C_{20}H_{17}N_2O_4$ $[M+H]^+$ m/z 349.1188, found m/z 349.1187.

4.10. 7-Ethyl-10-hydroxycamptothecin SN-38

Yield 80%. Mp = 216–218 °C (lit. mp = 215–217 °C). IR (neat): ν_{max} (cm^{-1}) 3214, 1737, 1651, 1584, 1568, 1506, 1466, 1251, 1168, 1053, 1037, 836. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.3 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 4.8 Hz, 2H), 7.23 (s, 1H), 6.49 (s, 1H), 5.40 (s, 1H), 5.22 (s, 1H), 3.04 (q, J = 7.6 Hz, 2H), 1.84 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3, 156.6, 156.4, 149.8, 148.5, 146.1, 143.3, 142.4, 131.2, 127.9, 127.7, 122.0, 117.7, 104.5, 95.5, 72.1, 65.0, 49.1, 29.9, 22.0, 13.0, 7.5. HRMS calcd for $C_{22}H_{21}N_2O_5$ $[M+H]^+$ m/z 393.1450, found m/z 393.1459.

The catalyst's preparation followed by Dixon's procedure.[17]

1-[(8*S*,9*S*)-1-Benzyl-6′-methoxycinchonan-1-ium-9-yl]-3-[4-(methyl)phenyl]urea bromide **13a**. Mp = 187–189 °C (decomp.). IR (neat): ν_{max} (cm^{-1}) 3248, 2953, 1681, 1661, 1544, 1508, 1314, 1222, 1024, 816, 702, 510. ^{1}H NMR (400 MHz, MeOD) δ 8.78 (s, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 16.4 Hz, 2H), 7.61 (s, 2H), 7.56 (s, 3H), 7.50 (d, J = 9.3 Hz, 1H), 7.22 (d, J = 7.1 Hz, 2H), 7.07 (s, 2H), 6.38 (s, 1H), 6.01–5.75 (m, 1H), 5.33–5.12 (m, 3H), 4.91 (s, 1H), 4.56 (s, 1H), 4.00 (s, 3H), 3.86 (s, 1H), 3.53–3.36 (m, 2H), 2.75 (s, 1H), 2.28–2.04 (m, 6H), 1.96 (s, 1H), 1.35–1.20 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 160.7, 156.7, 148.6, 145.7, 145.5, 137.5, 137.3, 134.6, 134.0, 132.0, 131.8, 130.5, 130.4, 128.9, 128.8, 124.2, 120.7, 120.6, 118.2, 102.5, 68.8, 67.4, 62.1, 56.6, 51.7, 50.8, 38.6, 28.6, 28.2, 25.6, 20.8. HRMS calcd for $C_{35}H_{39}N_4O_2$ $[M-Br]^+$ m/z 547.3073, found m/z 547.3070.

1-[(8*S*,9*S*)-1-Benzylcinchonan-1-ium-9-yl]-3-[4-(methyl)phenyl] urea bromide **13b**. Mp = 179–181 °C (decomp.). IR (neat): ν_{max} (cm^{-1}) 3247, 1680, 1598, 1547, 1510, 1458, 1308, 1214, 933, 817, 763, 507. ^{1}H NMR (400 MHz, MeOD) δ 8.97 (s, 1H), 8.58 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.00–7.76 (m, 3H), 7.68 (s, 2H), 7.58 (s, 3H), 7.12 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 7.9 Hz, 2H), 6.57 (s, 1H), 5.74 (ddd, J = 16.0, 10.7, 5.3 Hz, 1H), (d, J = 17.8 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 5.02 (d, J = 13.1 Hz, 1H), 4.94–4.89 (m, 1H), 4.06 (s, 1H), 3.94–3.69 (m, 2H), 3.41–3.34 (m, 1H), 2.79–2.56 (m, 1H), 2.21 (s, 3H), 2.15–2.02 (m, 1H), 2.00–1.77 (m, 2H), 1.64 (s, 1H), 1.48–1.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 150.8, 148.4, 145.9, 136.5, 135.0, 133.8, 132.0, 130.6, 130.5, 129.6, 129.3, 129.1, 127.6, 127.4, 126.5, 123.1, 120.4, 119.6, 118.6, 69.5, 64.9, 55.7, 51.9, 47.8, 37.7, 27.2, 26.8, 23.7, 20.7. HRMS calcd for $C_{34}H_{37}N_4O$ $[M-Br]^+$ m/z 517.2967, found m/z 517.2954.

A. Supplementary data

Supplementary data (NMR spectra for all of the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.04.013.

References

1. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; Mcphail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890.
2. (a) Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873–14878; (b) Li, Q. Y.; Zu, Y. G.; Shi, R. Z.; Yao, L. P. *Chemistry* **2006**, *13*, 2021–2039; (c) Curran, D. P. C. R. *Chimie* **2008**, *11*, 1574–1583.
3. (a) Du, W. *Tetrahedron* **2003**, *59*, 8649–8687; (b) Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140–2141.
4. (a) Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R. L. *J. Org. Chem.* **1997**, *62*, 6588–6597; (b) Imura, A.; Itoh, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2285–2291; (c) Imura, A.; Itoh, A. M.; Miyadera, A. *Chem. Pharm. Bull.* **1998**, *46*, 1878–1880; (d) Wani, M. C.; Nicholas, A. W.; Wall, M. E. *J. Med. Chem.* **1987**, *30*, 2317–2319.
5. (a) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *Tetrahedron Lett.* **1989**, *30*, 2639–2640; (b) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 27–31; (c) Watanable, T.; Tsuboi, Y.; Nomura, S. *Chem. Asian J.* **2013**, *8*, 630–638; (d) Comins, D. L.; Baevsky, M. F.; Hao, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971–10972; (e) Comins, D. L.; Hao, H.; Gao, J. H. *Tetrahedron Lett.* **1994**, *35*, 5331–5334; (f) Comins, D. L.; Saha, J. K. *Tetrahedron Lett.* **1995**, *36*, 7995–7998; (g) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255–4257; (h) Peters, R.; Althaus, M.; Nagy, A. L. *Org. Biomol. Chem.* **2006**, *4*, 498–509.
6. (a) Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142–6143; (b) Curran, D. P.; Ko, S. B.; Josien, H. *Angew. Chem. Int. Ed.* **1995**, *107*, 2948–2950; (c) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67–83; (d) Jew, S.; Ok, K.; Kim, H.; Kim, M. G.; Kim, J. M.; Hah, J. M.; Cho, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 1245–1248; (e) Akiyama, R.; Matsuki, N.; Nomura, H.; Yoshida, H.; Yoshida, T.; Kobayashi, S. *RSC Adv.* **2012**, *2*, 7456–7461; (f) Zhao, L.; Xiong, F. J.; Chen, W. X.; Chen, F. E. *Synthesis* **2011**, *24*, 4045–4049; (g) Liu, G. S.; Dong, Q. L.; Yao, Y. S.; Yao, Z. J. *Org. Lett.* **2008**, *10*, 5393–5396; (h) Zhou, H. B.; Liu, G. S.; Yao, Z. J. *Org. Lett.* **2007**, *9*, 2003–2006.
7. (a) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; (b) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923–2925; (c) Yabu, K.; Masumoto, S.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *Heterocycles* **2003**, *59*, 369–385; (d) Kuang, Y. Y.; Niu, J. Z.; Chen, F. E. *Helv. Chim. Acta* **2010**, *93*, 2094–2099.
8. (a) Chen, B. C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, 1–63; (b) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715–3717; (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934.
9. Hiroya, K.; Kawamoto, K.; Sakamoto, T. *Synlett* **2006**, 2636–2640.
10. (a) Zhang, L. P.; Bao, Y.; Kuang, Y. Y.; Chen, F. F. *Helv. Chim. Acta* **2008**, *10*, 2057–2061; (b) Watanable, T.; Odagi, M.; Furukori, K.; Nagasawa, K. *Chem. Eur. J.* **2014**, *20*, 591–597.
11. (a) Wani, M. C.; Ronman, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554–560; (b) Yang, S.; Zhang, W. N.; Zhou, Y. J.; Yao, J. Z.; Yu, J. X.; Sheng, C. Q. *Chin. J. Med. Chem.* **2004**, *14*, 242–244; (c) Yang, S.; Zhang, W. N.; Zhou, Y. J.; Yao, J. Z.; Ji, H. T. *Chin. J. Med. Chem.* **2004**, *14*, 106–108; (d) Miao, Z. Y.; Zhang, W. N.; Yao, J. Z.; Sheng, C. Q.; Song, Y. L.; Zhang, M. *Chin. J. Med. Chem.* **2005**, *15*, 244–246.
12. Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611–617.
13. (a) Malecki, N.; Houssin, R.; Henichart, J. P.; Couturier, D.; Petra, F.; Legentil, L.; Rigo, B. *J. Heterocycl. Chem.* **2003**, *40*, 45–50; (b) Finkelstein, J.; Brossi, A. *Org. Synth. Collect.* **1988**, 471–473; (c) Brunin, T.; Legentil, L.; Henichart, J. P.; Rigo, B. *Tetrahedron* **2006**, *62*, 3959–3968.
14. Acocella, M. R.; Mancheno, O. G.; Bella, M.; Jorgensen, K. A. *J. Org. Chem.* **2004**, *69*, 8165–8167.
15. (a) Gong, B.; Meng, Q. W.; Su, T.; Gao, Z. X. *Youji Huaxue* **2010**, *30*, 401–408; (b) Jiang, J. J.; Huang, J.; Wang, D.; Zhao, M. X.; Wang, F. J.; Shi, M. *Tetrahedron: Asymmetry* **2010**, *21*, 794–799.
16. Zhang, L. P.; Bao, Y.; Chen, F. E. *Zhongguo Yiyao Gongye Zazhi* **2008**, *39*, 481–483.
17. (a) Johnson, K.; Rattley, M.; Sladojevich, F.; Barber, D. M.; Nunez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492–2495; (b) Sladojevich, F.; Arriba, A. F.; Ortin, I.; Yang, T.; Ferrali, A.; Paton, R. S.; Dixon, D. J. *Chem. Eur. J.* **2013**, *19*, 14286–14295.